REMARKS

Applicants respectfully request reconsideration of this application.

I. STATUS OF THE CLAIMS

Following entry of this amendment, claims 11-36, 40-45, 46-49, and 51-117 are pending. Claims 37, 38, and 50, were cancelled, without prejudice or disclaimer thereof; claims 11, 23, 35, 40, and 42-44 were amended; and claims 59-117 were added to the application.

Claims 11, 23, 35, 40, and 42-44 were amended to define the phrase "poorly soluble" as a drug having a solubility in a liquid dispersion medium of less than about 10 mg/ml. *See e.g.*, page 25, lines 1-3, of the application. In addition, the claims were amended to define the phrase "effective average of less than about 1000 nm" as "at least 50% of the particles have a particle size of less than about 1000 nm." *See e.g.*, page 13, lines 2-11, of the application. Finally, claim 43 was amended to state that the milled drug had a particle size of less than about 1000 nm. *See e.g.*, page 13, lines 1-2, of the application.

New claims 59-70 recite preferred particle sizes for the compositions and methods. Exemplary support for this subject matter can be found in the specification at, for example, page 13, lines 1-12. New claims 71-117 recite the subject matter of original claims 14, 15, and 18-22. The chart below lists the new claim, the claim from which the new claim depends, and exemplary support for the new claim.

New Claim	Dependency	Exemplary Support
71, 77	Depend from claims 19 and 30, respectively, which recite aggregates of nanoparticulate drug and surface stabilizer having a MMAD of about 2 to about 6 microns.	Original claims 14 and 25
72, 78	Depend from claims 19 and 30, respectively, which recite aggregates of nanoparticulate drug and surface stabilizer having a MMAD of about 2 to about 6 microns.	Original claims 15 and 26
73, 79	Depend from claims 20 and 31, respectively, which recite aggregates of nanoparticulate drug and surface stabilizer having a MMAD of less than about 2 microns.	Original claims 14 and 25

New Claim	Dependency	Exemplary Support
74, 80	Depend from claims 20 and 31, respectively, which recite aggregates of nanoparticulate drug and surface stabilizer having a MMAD of less than about 2 microns.	Original claims 15 and 26
75, 81	Depend from claims 22 and 33, respectively, which recite aggregates of nanoparticulate drug and surface stabilizer having a MMAD of about 30 to about 60 microns.	Original claims 14 and 25
76, 82	Depend from claims 22 and 33, respectively, which recite aggregates of nanoparticulate drug and surface stabilizer having a MMAD of about 30 to about 60 microns.	Original claims 15 and 26
83, 90, 97, 104, and 111	Depend from claims 35, 40, 42, 43, and 44, respectively, which recite a dry powder nanoparticulate composition (claim 35) and methods of making dry powder nanoparticulate drug aerosols (claims 40-44).	Original claims 14 and 25
84, 91, 98, 105, and 112	Depend from claims 35, 40, 42, 43, and 44, respectively.	Original claims 15 and 26
85, 92, 99, 106, and 113	Depend from claims 35, 40, 42, 43, and 44, respectively.	Original claims 18 and 29
86, 93, 100, 107, and 114	Depend from claims 35, 40, 42, 43, and 44, respectively.	Original claims 19 and 30
87, 94, 101, 108, and 115	Depend from claims 35, 40, 42, 43, and 44, respectively.	Original claims 20 and 31
88, 95, 102, 109, and 116	Depend from claims 35, 40, 42, 43, and 44, respectively.	Original claims 21 and 32
89, 96, 103, 110, and 117	Depend from claims 35, 40, 42, 43, and 44, respectively.	Original claims 22 and 33

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. SUMMARY OF THE INVENTION

The claimed invention is directed to dry powder aerosols of nanoparticulate compositions for pulmonary and nasal delivery consisting of aggregates of nanoparticulate drug, or aggregates of diluent comprising embedded nanoparticulate drug. Essentially every inhaled particle of the aerosols contains at least one nanoparticulate drug particle. This is not shown or suggested by the cited prior art.

Using the compositions of the invention, essentially water-insoluble drugs can be delivered to the deep lung. This is either not possible or extremely difficult using aerosol formulations of micronized water-insoluble drugs. Deep lung delivery requires a MMAD of less than or equal to about 2 microns. A drug particle having such an aerodynamic diameter and a density of about 1 will have a geometric diameter of less than or equal to about 2 microns. The relationship between aerodynamic diameters and geometric particle sizes is represented by the following equation:

$$\text{Aerodynamic diameter} = \text{geometric diameter } (\text{density})^{1/2}$$

See col. 11, lines 18-46, of Edwards et al.; and P. Byron, "Aerosol Formulation, Generation, and Delivery Using Nonmetered Systems," *Respiratory Drug Delivery*, 144-151, at 145 (CRC Press, 1989) (EXHIBIT 1).

A geometric particle size of less than or equal to about 2 microns is difficult or impossible to achieve with jet milling; *i.e.*, the process used to obtain micronized drugs. The present invention overcomes this difficulty by incorporating nanoparticulate sized drug particles into aggregates having a variety of MMAD sizes, thus allowing for targeting of drugs to various regions of the respiratory tract, including deep lung delivery.

Deep lung delivery is necessary for drugs that are intended for systemic administration because deep lung delivery allows rapid absorption of the drug into the bloodstream via the alveoli, thus enabling rapid onset of action. *See* page 23, lines 11-16, of the application.

Finally, the dry nanoparticulate powder aerosols of the present invention enable rapid nasal absorption. When delivered to the nasal mucosa, such aerosol compositions dissolve and are absorbed more rapidly and completely than micronized drug aerosol compositions, which may be cleared by the mucociliary mechanism prior to drug dissolution and absorption. *See* page 24, lines 15-18, of the application.

III. OFFICE ACTION

A. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 11, 23, 35, 37, 40, and 42-44 were rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. Office Action at page 2. Applicants respectfully traverse this ground for rejection.

The Examiner stated that claims 11, 23, 35, 37, 40, and 42-44 were indefinite for failing to define the phrase "poorly soluble." Office Action at page 2. Claim 37 has been canceled and claims 11, 23, 35, 40, and 42-44 have been amended to recite that by "poorly soluble" it is meant that the drug has a solubility in at least one liquid dispersion medium of less than about 10 mg/ml, Support for this amendment can be found in the specification at, for example, page 25, lines 1-3. The liquid dispersion medium is not limited to water. For example, the application states that the drug contained in the composition of the invention "is dispersible in at least one liquid medium." *See* page 24, line 29, through page 25, line 3, of the application.

Because Applicants claims are definite, withdrawal of this ground for rejection is courteously requested.

B. Rejection of Claims Under 35 U.S.C. § 102(b) Over WO 95/27475 to Adjei et al.

Claim 42 was rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Adjei et al., WO 95/27475. In support of this ground for rejection, the Examiner stated that "Adjei et al. disclose claim 42 of applicant's invention on page 1, lines 26-31." Office Action at page 3. Applicants respectfully traverse this ground for rejection.

Adjei et al. describe a process and apparatus for the continuous milling of aerosol pharmaceutical formulations containing solids by milling in an aerosol propellant. The process comprises milling the solid component of a dry powder aerosol directly in the material which serves as the propellant in the final aerosol formulation, thereby avoiding the step of removing the milling medium. *See* page 2, lines 25-29, of Adjei et al. Each ingredient added to the aerosol formulation during the processing becomes a part of the final formulation. *See* page 3, lines 30-35, of Adjei et al.

This reference does not teach the critical limitations of claim 42; namely, the effective average particle size of the milled active agent of less than about 1 micron. Specifically, Adjei et al. refer to milling to obtain a desired particle size which is "generally below about 10 microns." *See* page 9, lines 11-13; and Examples 1-4 (no other examples are described) at page 9, lines 22-23 and 30-31; and page 10, lines 5-6 and 13-14, of Adjei et al. This is **10 times** the size specified in Applicant's claims, and refers to a micronized drug product and not a nanoparticulate drug product.

Applicant's claimed invention does not encompass micronized drug products, as all of the claims recite a drug having an effective average particle size of less than about 1 micron, defined as at least 50% of the particles having a particle size of less than 1 micron. Accordingly, Adjei et al. do not teach or suggest the claimed invention and, accordingly, withdrawal of this ground for rejection is courteously requested.

C. Rejection of the Claims Under 35 U.S.C. § 102(e)

1. Edwards et al., U.S. Patent No. 5,985,309

Claims 11-14, 16-25, 27-33, 40, 41, 44, and 45 were rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Edwards et al., U.S. Patent No. 5,985,309. In support of this ground for rejection, the Examiner stated that Edwards et al. "disclose particles incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system." Office Action at page 3. Applicants respectfully traverse this ground for rejection.

a. Summary of Edwards et al.

Edwards et al. is directed to a particulate composition for inhalation comprising a **micronized** drug and a surfactant. *See* the Abstract and col. 5, lines 5-9, of Edwards et al. This reference does not teach the use of nanoparticulate drugs in dry powder aerosol formulations. Rather, this reference refers to the use of aggregates of dry micronized drug having a geometric particle size of from a mean of between 5 and 30 microns, and an aerodynamic particle size of from 1 to 5 microns (e.g., particles having a density <<1). *See*

col. 4, lines 1-7; col. 5, lines 10-13; and col. 6, lines 1-10, of Edwards et al. This does not teach or suggest the claimed invention.

b. Edwards et al. Do Not Teach Applicants' Claimed Drug Particle Sizes

Applicants' amended claims recite dry powder nanoparticulate drug aerosols in which at least 50% of the drug particles have a geometric particle size of less than about 1 micron, which form aggregates having a particle size of less than about 100 microns in diameter. This is not taught or suggested by Edwards et al., as this reference does not teach or suggest the use of nanoparticulate drugs in dry powder aerosol compositions.

The nanoparticulate drug particle size is critical to the invention, as it is this element of the invention which allows incorporation of drug particles into aggregates having a variety of MMAD sizes, thus allowing for targeting of drugs to various regions of the respiratory tract, including deep lung delivery. The ability to obtain very small drug particle sizes which can "fit" in a range of aggregate particle sizes allows more effective and more efficient (*i.e.*, dose uniformity) targeting to the desired delivery region. This is not possible using micronized drug, as the particle size of such drugs is too large to "fit" into smaller aggregate particle sizes, i.e., aggregate particle sizes of less than or equal to about 2 microns. Moreover, even when micronized drug is incorporated into larger aggregate particle sizes, the resultant aerosol formulation does not result in the rapid and efficient drug delivery enabled by the nanoparticulate aerosol formulations of the invention. *See* page 23, line 26, through page 24, line 6, of the application.

Furthermore, the dry nanoparticulate powder aerosols of the present invention are spherical and can be made smaller than micronized material, thereby producing aerosol compositions having better flow and dispersion properties, and capable of being delivered to the deep lung. *See* page 24, lines 11-14, of the application.

Because Edwards et al. do not teach dry powder aerosols comprising nanoparticulate drug particles, this reference does not teach or suggest the claimed invention. Withdrawal of this ground for rejection is respectfully requested.

2. Wiedmann et al., U.S. Patent No. 5,747,001

Claims 37, 38, and 50 were rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Wiedmann et al., U.S. Patent No. 5,747,001. Office Action at page 4. Applicants respectfully traverse this ground for rejection.

While Applicants respectfully disagree with this ground for rejection, claims 37, 38, and 50 have been cancelled for the sole purpose of advancing the prosecution of this case. Applicants reserve the right to prosecute the subject matter of these claims in this or another application.

As this ground for rejection is moot, withdrawal thereof by the Examiner is courteously requested.

D. Rejection of the Claims Under 35 U.S.C. § 103(a)

1. Adjei et al. and Liversidge et al., EP 499 299

Claims 42 and 43 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Adjei et al. and Liversidge et al., EP 499 299. Office Action at page 5. Applicants respectfully traverse this ground for rejection.

Claims 42 and 43 are directed to methods of making dry powder nanoparticulate drug aerosols under non-pressurized conditions (claim 42) and under pressurized conditions (claim 43). The methods comprise milling a poorly soluble crystalline drug in a non-aqueous medium, followed by evaporation of the non-aqueous medium to obtain the dry powder comprising nanoparticulate drug.

a. Examiner's Basis for the Rejections

In support of this ground for rejection the Examiner stated that while "Adjei et al. do not disclose the pressurized conditions of . . . claim 43, . . . Liversidge et al. disclose . . . that ambient pressures are typical of ball mills, attritor mills and vibratory mills and the processing pressures of up to about 20 psi are typical of media milling." Office Action at page 5.

b. The Cited References Do Not Teach or Suggest Applicants' Claimed Aerosols

Adjei et al. was discussed above. This reference does not teach or suggest Applicants' claimed nanoparticulate drug sizes.

Liversidge et al., EP 499 299, is the European equivalent to co-owned U.S. Patent No. 5,145,684, which is referenced in the present application at page 7, lines 9-11; page 18, lines 18-19; and page 26, lines 5-6. Liversidge et al. describe non-aerosol preparations of submicron sized water-insoluble drugs. This reference does not remedy the deficiencies of Adjei et al., in that it does not teach or suggest aerosol dosage forms comprising a nanoparticulate drug.

Liversidge et al. is limited to non-aerosol dosage forms. The present invention is an improvement over the invention of Liversidge et al., as it has now been discovered that nanoparticulate drugs can be effectively incorporated in aerosol dosage forms, including dry powder dosage forms. Aerosol dosage forms can be difficult to design, as pulmonary drug delivery strategies present many difficulties for the delivery of macromolecules. Such difficulties include protein denaturation during aerosolization, excessive loss of inhaled drug in the oropharyngeal cavity (often exceeding 80%), poor control over the site of deposition, lack of reproducibility of therapeutic results owing to variations in breathing patterns, the frequent too-rapid absorption of drug potentially resulting in local toxic effects, and phagocytosis by lung macrophages. *See* Edwards et al. at col. 1, lines 33-42.

In addition, dry powder aerosols can be even more difficult to design than aqueous aerosols as dry powder aerosols can have a tendency to aggregate (col., 1, lines 47-51, of Edwards et al.), and may have poor flowability and aerosolization properties, leading to relatively low respirable fractions of aerosol (col. 3, lines 14-20, of Edwards et al.).

Accordingly, there is no motivation to combine the teachings of Adjei et al. and Liversidge et al. to obtain the claimed invention, as Liversidge et al. is limited to non-aerosol dosage forms, and Adjei et al. teaches away from using nanoparticulate drugs in dry powder aerosols. Withdrawal of this ground for rejection is respectfully requested.

2. Edwards et al., U.S. Patent No. 5,985,309

Claims 11-34, 40, 41, 44, 45, 47, 48, and 51-58 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Edwards et al. Office Action at page 5. Applicants respectfully traverse this ground for rejection.

In support of this ground for rejection the Examiner stated that while Edwards et al. "do not disclose the particle size of the active substance . . . Edwards et al. meets applicant's particle size limitations because Edwards et al. discloses powders comprised of active and additional excipients [which] when combined yield a product size of 1-3 microns." *See* page 5 of the Office Action.

As acknowledged by the Examiner, Edwards et al. "**do not disclose the particle size of the active substance**." Moreover, the methods described in the specification of Edwards et al. for obtaining the described dry powder aerosols do not encompass obtaining nanoparticulate drug particles for incorporation into dry powder aerosols.

As discussed above, the particle size of the active agent is a critical limitation of the invention, as it is this limitation which results in dry powder aerosols having superior properties as compared to prior art dry powder aerosols, such as those described by Edwards et al. For example, nanoparticulate drug particles enable dry powder aerosols for deep lung delivery, as the nanoparticle drug particles can "fit" in aggregate particle sizes of less than about 2 microns. This is not the case for micronized drug. Moreover, even when micronized drug is incorporated into larger aggregate particle sizes, the resultant aerosol formulation does not result in the rapid and efficient drug delivery enabled by the nanoparticulate aerosol formulations of the invention. *See* page 23, line 26, through page 24, line 6, of the application.

In addition, the ability to obtain very small drug particle sizes which can "fit" in a range of aggregate particle sizes allows more effective and more efficient (*i.e.*, dose uniformity) targeting to the desired delivery region.

Finally, the dry nanoparticulate powder aerosols of the present invention are spherical and can be made smaller than micronized material, thereby producing aerosol compositions having better flow and dispersion properties, and capable of being delivered to the deep lung. *See* page 24, lines 11-14, of the application.

In addition, in response to the Examiner's statement regarding claims 47 and 48 (directed to a dosing regimen) that the "Examiner is unaware of any human beings who can inhale for longer than 15 seconds," the dosing regimen can consist of multiple breaths. For example, prior art aerosol formulations frequently required inhaling for 20 minutes or

more to obtain the desired therapeutic effects. *See e.g.,* page 7, lines 19-21, of the application. This was not accomplished in one breath; multiple breaths are required.

Because Edwards et al. do not teach dry powder aerosols comprising nanoparticulate drug particles, this reference does not teach or suggest the claimed invention. Withdrawal of this ground for rejection is respectfully requested.

3. Edwards et al., U.S. Patent No. 5,985,309, in Combination with Smith et al., U.S. Patent No. 5,785,049

Claims 11-36, 40, 41, 44, 45, 47-49, and 51-58 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Edwards et al. Office Action at page 6. Applicants respectfully traverse this ground for rejection.

In support of this ground for rejection the Examiner stated that while Edwards et al. "do not disclose [a] propellant . . . Smith et al. disclose an apparatus for dispersion of dry powder medicaments." Office Action at page 6. The Examiner concluded that it would have been obvious to modify Edwards et al. to use a propellant, such as suggested by Smith et al. Office Action at page 6.

Smith et al. do not remedy the deficiency of Edwards et al., in that this reference does not teach the use of **nanoparticulate** drugs in dry powder aerosol compositions. Accordingly, Edwards et al. in combination with Smith et al. fail to teach or suggest the claimed invention and, therefore, withdrawal of this ground for rejection is respectfully requested.

4. Wiedmann et al., U.S. Patent No. 5,747,001

Claims 37, 38, and 50 were rejected under 35 U.S.C. § 103(a) as being allegedly anticipated by Wiedmann et al., U.S. Patent No. 5,747,001. Office Action at page 7. Applicants respectfully traverse this ground for rejection.

While Applicants respectfully disagree with this ground for rejection, claims 37, 38, and 50 have been cancelled for the sole purpose of advancing the prosecution of this case. Applicants reserve the right to prosecute the subject matter of these claims in this or another application.

As this ground for rejection is moot, withdrawal thereof by the Examiner is courteously requested.

IV. CONCLUSION

Applicants respectfully request reconsideration of this application in view of the above amendments and remarks. This application is now in condition for allowance and early notice to that effect is respectfully solicited.

Should the Examiner have any questions or comments regarding the pending application or this Amendment, the Examiner is requested to call the undersigned at 202-672-5538.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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